Docket No.: 337348055US1

(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Sheffield et al.

Application No.: 10/731,892

Confirmation No.: 4677

Filed: December 9, 2003

Art Unit: 3766

For: METHODS FOR TREATING AND/OR COLLECTING INFORMATION REGARDING NEUROLOGICAL DISORDERS, INCLUDING LANGUAGE DISORDERS

Examiner: J. L. Reidel

DECLARATION OF JUSTIN HULVERSHORN, M.D., Ph.D. UNDER 37 C.F.R. SECTION 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Justin Hulvershorn, declare that:

(1) I am a citizen of the United States residing at 409 Highline Drive, Seattle, Washington 98109.

(2) I acted as a consultant for Northstar Neuroscience beginning in April, 2006, and became an employee of Northstar Neuroscience in October, 2006. My current position at Northstar Neuroscience is Research Manager.

(3) My relevant professional qualifications are listed on the attached curriculum vitae.

(4) I am familiar with existing deep brain stimulation (DBS) techniques used to treat neurological disorders. I am also familiar with cortical stimulation techniques that have been developed and are currently being developed by Northstar Neuroscience for treating neurological disorders.

(5) DBS is generally much more invasive than cortical stimulation because DBS requires that an electrode be passed through brain tissue until the electrode is located within deep brain tissue. Cortical stimulation is applied from electrodes implanted proximate to the dura mater surrounding the brain, but outside the cortical surface of the brain.

(6) A signal applied to a DBS electrode generates an electric field that extends a few to several millimeters from the DBS electrode. At most, the electric field generated by a DBS electrode might be expected to extend approximately 1 centimeter from the DBS electrode provided that the signal applied to the DBS electrode is quite strong. Hence, a signal applied by a DBS electrode does not directly stimulate, activate, or reach cortical structures. For instance, a DBS signal applied to the Intralaminar Nuclei (ILN) does not directly stimulate, activate, or reach Broca's area, Wernicke's area, or other cortical areas.

(7) DBS can trigger neural signal transfer along neuronal projections that extend away from deep brain neurons which themselves reside sufficiently close to the DBS electrode. Such neuronal projections can extend to distant cortical structures. However, activating or affecting distant cortical structures by way of intermediate neurons and/or neural projections as a result of a signal applied to a deep brain structure is not identical or equivalent to directly stimulating such cortical structures. In other words, applying a signal to a DBS electrode to generate neural signals that propagate to intermediate and possibly distant neuronal elements is not equivalent to affecting cortical neurons that are directly within the range of an electric field generated by an electrode positioned proximate to the dura mater and outside a cortical surface of the patient's brain.

(8) The commonly accepted mechanism(s) by which cortical stimulation achieves an intended effect are not identical to the commonly accepted mechanism(s) by which DBS achieves an intended effect relative to treating a given type of neurologic dysfunction. DBS has generally been believed to create a "virtual lesion" that disrupts, overrides, or shuts down normal neural signaling processes in deep brain neurons that reside sufficiently close (e.g., within 2 mm) to the DBS electrode to be directly affected by the DBS signal. The mechanism(s) by which direct cortical stimulation generates an intended effect can be much more complex, and can be completely independent of the generation of a "virtual lesion." Moreover, the generation of a cortical "virtual lesion" can result in unwanted or undesirable effects upon patient function.

(9) Efficacious stimulation parameters for cortical stimulation are generally not identical to those for DBS; typically, cortical stimulation parameters are substantially different from parameters used to treat patients using DBS. For a particular type of neurologic disorder or patient symptom, a given set or range of efficacious DBS stimulation parameters can have no beneficial effect, or result in an adverse effect, when used to treat the disorder or symptom using cortical stimulation.

(10) Even though DBS is generally much more invasive and commensurately carries significantly greater surgical risk than the implantation of a cortical stimulation electrode proximate to the dura mater outside a cortical surface of the patient's brain, many clinical trials using DBS are presently underway, including more than 20 of the trials identified in the attached trial listing. Thus, even in view of its expected invasiveness and greater risk of surgical complications, DBS is being used in these trials instead of cortical stimulation. This further indicates that cortical stimulation is not identical to or a simple substitute for DBS.

(11) U.S. Patent No. 5,938,688 to Schiff provides a representative example of the state of the art at the time of the invention by disclosing the ILN (which are deep brain structures)

as the preferred region to which electrical stimulation is to be applied, to the exclusion of other regions of the patient's brain.

(12) Based on the foregoing, many applications of cortical stimulation techniques are not equivalent to or otherwise interchangeable with DBS techniques; cortical stimulation techniques, therefore, are not readily substituted for existing DBS techniques. Furthermore, a practitioner's decision to select either cortical stimulation or DBS is not simply an arbitrary or obvious design consideration.

(13) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Justin Hulvershorn, M.D., Ph.D.

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Date: 11/5/07

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EDUCATION

M.D. University of Pennsylvania, May 2006

Ph.D. University of Pennsylvania, 2004
Department of Biochemistry and Molecular Biophysics,
"Imaging Neural Activity: Improved localization, quantitation, and temporal resolution using novel fMRI contrasts."

B.S. University of Virginia, 1996
Engineering with highest honors

WORK EXPERIENCE

SUMMER 1994: Worked on a six-member team installing the computer network for the new National Archives building in Bethesda, MD.

SUMMER 1995: Worked in the lab of Dr. Klaus Ley at the University of Virginia creating monoclonal cell lines expressing surface proteins involved in cell adhesion.

1996-1998: Boston Biomedical Research Institute: Research Associate performing fluorescent light and confocal microscopy to study smooth muscle contraction pathways. Maintained a PC/Mac/Unix computer network and all laboratory equipment.

2001-2004: Thesis work Designed and built hardware and software components of a near infrared spectroscopic system used to measure hemoglobin saturation changes in the human cortex during cognitive tasks. Constructed imaging coils and other hardware for use in MRI scanners to study neural activity. Designed custom software in C++, Matlab, and IDL for image analysis and data processing.

2005: Worked with a team from Drexel University and the University of Pennsylvania designing a haptic interface system to simulate ultrasound examination of the pregnant uterus for training of technicians.

2006: Consulting with two Seattle based neuromedical device companies

2006-7: Senior Scientist and Research Manager at Northstar Neuroscience

PUBLICATIONS

Hulvershorn J, Borthakur A, Bloy L, Gualtieri EE, Reddy R, Leigh JS, Elliot MA. $T_{1\rho}$ Contrast in Functional MRI. *Magnetic Resonance in Medicine.* In Press.

Hulvershorn J, Bloy L, Gualtieri EE, Leigh JS, Elliot MA. Temporal Resolving Power of Spin Echo and Gradient Echo fMRI at 3T with Apparent Diffusion Coefficient Compartmentalization. *Human Brain Mapping*, 25(2): 2005 June.

Hulvershorn J, Bloy L, Gualtieri EE, Leigh JS, Elliot MA. Spatial Sensitivity and Temporal Response of Gradient Echo and Spin Echo fMRI at 3 T using Peak Hemodynamic Activation Time. *NeuroImage*, 24(1): 216-23, 2005 Jan 1.

Elliott M.A., Gualtieri EE, Hulvershorn J, Ragland JD, Gur R. The Effects of Geometric Distortion Correction on Motion Realignment in fMRI. *Academic Radiology*. 11: 1005-1010, 2004 June.

Hulvershorn J, Bloy L, Leigh JS, Elliot MA. A continuous-wave optical spectroscopic system for use in MRI scanners for the measurement of changes in hemoglobin oxygenation states in humans. *Review of Scientific Instruments*. 74(9): 4150-7, 2003 Sep.

Miki A. Liu GT. Goldsmith ZG. Zhou L. Siegfried J. Hulvershorn J. Raz J. Haselgrove JC. Effects of check size on visual cortex activation studied by functional magnetic resonance imaging. *Ophthalmic Research*. 33(3): 180-4, 2001 May.

Hulvershorn J. Gallant C. Wang CA. Dessy C. Morgan KG. Calmodulin levels are dynamically regulated in living vascular smooth muscle cells. *American Journal of Physiology - Heart & Circulatory Physiology*. 280(3): H1422-6, 2001 Mar.

Dessy C. Matsuda N. Hulvershorn J. Sougnez CL. Sellke FW. Morgan KG. Evidence for involvement of the PKC-alpha isoform in myogenic contractions of the coronary microcirculation. *American Journal of Physiology - Heart & Circulatory Physiology*. 279(3): H916-23, 2000 Sep.

Menice CB. Hulvershorn J. Adam LP. Wang CA. Morgan KG. Calponin and mitogen-activated protein kinase signaling in differentiated vascular smooth muscle. *Journal of Biological Chemistry*. 272(40): 25157-61, 1997 Oct 3.

Search results for *deep brain stimulation [ALL-FIELDS]* are shown below.

Include trials that are no longer recruiting patients.

Search-Within-Results | Query Details | Map of locations

25 studies were found.

1. **Recruiting** Deep Brain Stimulation to Treat Symptoms of Parkinson's Disease
   Conditions: Parkinson Disease; Movement Disorders
2. **Not yet recruiting** Effects of Deep Brain Stimulation for the Treatment of Parkinson's Disease
   Condition: Parkinson
3. **Recruiting** Deep Brain Stimulation for Refractory Major Depression
   Condition: Major Depressive Disorder
4. **Recruiting** The Mood/Cognitive Effects of STN vs. GPi Deep Brain Stimulation in Parkinson's Disease
   Condition: Parkinson Disease
5. **Recruiting** Deep Brain Stimulation for Parkinson's Disease Trial
   Condition: Parkinson's Disease
6. **Recruiting** Efficacy and Safety of DBS of the GPi in Patients With Tardive Dystonia
   Conditions: Dystonia; Movement Disorder
7. **Recruiting** Deep Brain Stimulation in Treating Patients With Dystonia
   Condition: Dystonia
8. **Recruiting** Weight Changes in Parkinsonian Patients, Treated With Deep Brain Stimulation
   Condition: Parkinson Disease
9. **Recruiting** Deep Brain Stimulation for Treatment Resistant Depression
   Condition: Major Depressive Disorder
10. **Recruiting** Berlin Deep Brain Stimulation Depression Study
    Condition: Therapy Resistant Major Depression
11. **Not yet recruiting** Pallidal Stimulation and Gilles de la Tourette Syndrome
    Condition: Gilles de la Tourette Syndrome
12. **Recruiting** Pallidal Stimulation in Patients With Post-Anoxic and Idiopathic Dystonia
    Condition: Dystonia
13. **Recruiting** Pallidal Stimulation in Patients With Idiopathic Generalised Dystonia
    Condition: Dystonia
14. **Recruiting** Subthalamic Nucleus (STN) Stimulation and Obsessive-Compulsive Disorder (OCD)
    Condition: Obsessive Compulsive Disorder
15. **Recruiting** Double-Blind, Multicenter Study to Assess the Efficacy of Bilateral Pallidal Stimulation in Patients With Medically Refractory Primary Cervical Dystonia
    Condition: Cervical Dystonia

16. ☐ **Recruiting** Deep Brain Stimulation for Treatment-Refractory Major Depression
Condition: Depression
17. ☐ **Recruiting** DBS for Early Stage Parkinson's Disease
Condition: Parkinson's Disease
18. ☐ **Not yet recruiting** Controlled Trial of DBS in Early Patients With Parkinsons' Disease
Condition: Parkinson Disease
19. ☐ **Recruiting** "Electroencephalography (EEG) and Deep Brain Stimulation (DBS) in Epilepsy"
Condition: Epilepsy
20. ☐ **Recruiting** Bilateral Internal Pallidum Stimulation in Primary Generalized Dystonia
Conditions: Dystonia; Primary Generalized Dystonia
21. ☐ **Recruiting** STIMEP : Assessment of Subthalamic Nucleus Stimulation in Drug Resistant Epilepsy
Conditions: Epilepsy; Drug Resistant
22. ☐ **Recruiting** Study of Hypothalamic Metabolism in Spontaneous Cluster Headache Attacks
Condition: Cluster Headache
23. ☐ **Recruiting** Electrical Brain Stimulation to Reduce Epileptic Seizures
Condition: Temporal Lobe Epilepsy
24. ☐ **Not yet recruiting** Impact of Listening to Low Tones on Motor Function in Children With CP
Conditions: Cerebral Palsy; Hypertonia
25. ☐ **Recruiting** Can Erythopoietin Protect the Cerebral Blood Flow and Oxygenation During Simulated Dive?
Condition: Healthy

Display Selected Studies